REMARKS

Claims 1-38 are pending. Claims 4-8, 12, 13, and 16-38 are withdrawn from consideration. Claims 1 and 3 are amended herein. Claims 2 and 9-11 are canceled herein without prejudice. New claims 39-42 are presented herein. Accordingly, claims 1 and 3, as amended, and dependent claims therefrom and new claims 39-42, are presently under consideration.

Support for amendment to the claims is found throughout the specification and in the original claims. Specifically, support for amendment to claim 1 is found in original claim 1 and in paragraph [10]. Support for amendment to claim 3 is found in original claims 1 and 2. No issue of new matter is introduced by these amendments.

Support for new claims 39-42 is found in the original claims and throughout the specification. Specifically, support for new claim 39 is found, for example, in paragraph [37]. Support for new claim 40 is found, for example, in paragraphs [8] and [13]. Support for new claim 41 is found, for example, in paragraphs [8] and [17]. Support for new claim 42 is found, for example, in paragraphs [105] and Figure 1. No issue of new matter is introduced by these amendments.

The Specification is amended herein to correct clerical errors identified therein. More specifically, paragraphs [8], [27], [29], and [34] are amended herein to correct clerical errors. No issue of new matter is hereby introduced.

Information Disclosure Statement

The Examiner has indicated that the Information Disclosure Statement (IDS) filed 15 January 2004 allegedly fails to comply with the provisions of 37 CFR 1.97, 1.98, and MPEP § 609. Although Applicant believes that a copy of the reference listed as AI, which was originally submitted in the context of an IDS filed in connection with the parent application 10/042,527, was submitted to United States Patent Office, a copy of this reference is submitted herewith so as to clarify the record. Applicant notes, however, that the reference listed as AI was improperly cited in the IDS filed in connection with the parent application as a result of a clerical error whereby the name of the publisher was mistakenly listed instead of the journal name in which the reference was published. This clerical error is rectified herein by filing a Second Supplemental IDS, wherein the AI reference is properly listed, and to place

a copy of the AI reference (Asano et al. 2000, Tetrahedron: *Asymmetry* 11:1645) in the application file, along with a new reference for the Examiner's consideration, which is listed as BA.

Rejections 35 USC § 112

Claims 1-3, 9-11, 14, and 15 have been rejected under 35 U.S.C. §112, first paragraph, for allegedly containing subject matter not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors were in possession of the claimed invention at the time the application was filed. The rejection appears to be based on recitation of the phrase "inhibitor of glycolipid synthesis". The Examiner acknowledges that the specification provides a detailed description and reduction to practice using imido sugar compounds capable of glucosylceramide synthase. Claims 2 and 9-11 are canceled herein, thereby obviating the rejection of these claims. Claim 1 and dependent claims therefrom have been amended to clarify that the inhibitor of glycolipid synthesis is an imido sugar capable of inhibiting glucosylceramide synthase. Instant claims 1, 3, 14, and 15 and new claims 39-42 are, therefore, believed to be directed to subject matter for which the specification presents ample written description. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the rejection of claims 1, 3, 14, and 15 under 35 U.S.C. §112, first paragraph.

Claims 1-3, 9-11, 14, and 15 are rejected under 35 U.S.C. §112, first paragraph, on the basis as understood, that the claimed invention purportedly lacks sufficient enablement. Claims 2 and 9-11 have been cancelled, thereby obviating any rejection of these claims. Instant claim 1 and dependent claims therefrom are amended to be directed to a method for reducing accumulation of glucosylceramide-containing glycolipids in a patient afflicted with a glycolipid storage-related disorder, wherein the method comprises administering an inhibitor of glycolipid synthesis in combination with an agent capable of increasing the rate of glycolipid degradation, wherein said inhibitor of glycolipid synthesis is an imido sugar capable of inhibiting glucosylceramide synthase and is administered in an amount effective to reduce accumulation of glucosylceramide-containing glycolipids in said patient, and the agent capable of increasing the rate of glycolipid degradation is glucocerebrosidase or bone marrow transplantation.

In view of the above, the references cited by the Examiner that relate to gene therapy, including Verma et al. (1997, Nature 389:239), Marshall et al. (1995, Science 269:1050), Orkin et al. (1995, Report and Recommendations of the Panel to assess the NIH Investment in Research on Gene Therapy), Ross et al. (1996, Human Gene Therapy 7:1781), and Rubanyi et al. (2001, Mol. Aspects Med. 22:113) no longer pertain to the instant invention.

As stated by the Examiner at page 8 of the Office Action "the art teaches treatment of type I Gaucher disease by administration of glucocerebrosidase or bone marrow transplantation". One of skill in the art would also appreciate that patients with other glycoplid storage-related disorders typified by systemic storage defects may also benefit from the present method, which is directed to reducing accumulation of glucosylceramide-containing glycolipids in a patient afflicted with a glycolipid storage-related disorder. Such glycoplid storage-related disorders exhibiting systemic storage defects include, for example, Gaucher's disease, Sandhoff's disease, Fabry's disease and Tay-Sach's disease.

Sandhoff's disease is characterized by the accumulation of lipids in the brain and other organs of the body. A number of the symptoms of Sandhoff's disease are, therefore, related to systemic deposition of lipids. Fabry's disease is also associated with deposition of lipids in a variety of organ systems, including the eye, the circulatory system, and the kidneys. Tay Sach's disease is associated with a variety of symptoms, including loss of muscle tone and motor skills, which reflect systemic deposition of lipids.

Thus, in addition to the symptoms associated with inappropriate lipid deposition in the central nervous system, the above-mentioned glycolipid storage-related disorders are also known to affect organ systems other than the nervous system. In view of the above, the methods of the present invention are clearly applicable to patients with Sandhoff's disease, Fabry's disease and Tay-Sach's disease, as well as Gaucher's disease, because patients with these diseases suffer from symptoms related to systemic glycolipid deposition. The methods of the present invention may, therefore, be used advantageously to reduce accumulation of glucosylceramide-containing glycolipids in a patient afflicted with a glycolipid storage-related disorder associated with systemic glycolipid deposition.

Moreover, the examples of the present invention which demonstrate that NB-DNJ mediates an increase in the half-life of Ceredase™, provide compelling evidence that shows a combination of NB-DNJ and Ceredase™, for example, is of utility when administered to a

subject with Gaucher's disorder. One of skill in the art would recognize that extending the biological half-life of an agent elongates the temporal window in which such an agent is active, which in turn, enhances the activity of an agent administered to a subject. Moreover, a skilled practitioner would also appreciate that increasing peak activity is correlated with enhanced activity of the agent in a subject. See Table I. By extension, such evidence is applicable to other glycolipid storage-related disorders, such as Sandhoff's disease, Fabry's disease and Tay-Sach's disease.

Notably, the examples of the present invention also demonstrate that in a mouse model of Sandhoff's disease, Sandhoff mice respond favorably to a combination of NB-DNJ and bone marrow transplantation. In short, Sandhoff mice to which a combination of NB-DNJ and bone marrow transplantation is administered survive longer than counterparts to which bone marrow transplantation alone is administered. Thus, despite the Examiner's assertions that these results are only applicable to a subject afflicted with Sandhoff's disease, a skilled practitioner would predict that a glycolipid storage-related disorder shown to respond favorably to bone marrow transplantation would also respond favorably to the instant method. In view of the amendments to the claims and Applicant's arguments, the Examiner is respectfully requested to reconsider and withdraw the rejection of the instant claims under 35 U.S.C. §112, first paragraph.

Claims 2 and 3 have been rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. Claim 2 has been canceled and instant claim 3 depends from claim 1. In view of the above amendments to the claims, the rejection of these claims under 35 U.S.C. §112, second paragraph is rendered moot.

In view of the above, the Examiner is respectfully requested to reconsider and withdraw the rejection of the instant claims under 35 U.S.C. §112.

Rejection Under the Judicially Created Doctrine of Obviousness-Type Double Patenting

Claims 1-3, 9-11, 14, and 15 have been rejected on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 1 and 8 of U.S. Patent No. 6,696,059. Claims 2 and 9-11 are cancelled herein, thereby nullifying the

rejection of these claims under the judicially created doctrine of obviousness-type double patenting. A Terminal Disclaimer is attached hereto, the filing of which is believed to overcome the above rejection of claims 1, 3, 14, and 15 of the present invention under the judicially created doctrine of obviousness-type double patenting.

Rejection Under 35 U.S.C. § 102

Claims 1-3, 9-11, 14, and 15 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by any one of Platt et al. (1998; IDS AF), Platt and Butters (1998; IDS AO), or Aerts et al. (1998; IDS AH). It is the Examiner's opinion that each of the cited references allegedly teaches a method of treating glycolipid storage-related disorders comprising administering an inhibitor of glycolipid synthesis. The Examiner also maintains that each of the references allegedly contemplates that the method of treating with an inhibitor of glycolipid synthesis can further comprise an agent capable of increasing the rate of glycolipid degradation. Applicants disagree with the Examiner's position. Applicants respectfully submit that the present invention exemplifies a method for 1) reducing accumulation of glucosylceramide-containing glycolipids; 2) maintaining reduced levels of glycolipids; 3) augmenting glucocerebrosidase activity; 4) increasing the rate of glycolipid degradation; or 5) for improving survival in a patient afflicted with a glycolipid storage-related disorder, wherein the method is directed to administering a combination of an imido sugar capable of inhibiting glucosylceramide synthase [e.g., N-butyldeoxynojirimycin (NB-DNJ)] and either glucocerebrosidase or bone marrow transplantation to the patient. The present invention is based on the surprising result that NB-DNJ can act synergistically with either enzymes involved in glycolipid degradation (e.g., glucocerebrosidase) or transplanted bone marrow. None of the prior art documents cited by the Examiner suggest that NB-DNJ acts synergistically with either enzymes involved in glycolipid degradation or transplanted bone marrow.

Indeed, Platt et al. [1998; IDS AF; United States Patent Number (USPN) 5,786,368] state that NB-DNJ is known to be an inhibitor of lysosomal glucocerebrosidase, an enzyme required for the cleavage of Glc-Cer to glucose and ceramide. See column 10, lines 46-50. Moreover, Platt et al. teach that the N-butyl derivative of DNJ acts as an **inhibitor of glucocerebrosidase** in a cellular environment. See column 10, lines 50-56. Also provided

by Platt et al. is direct experimental evidence demonstrating that NB-DNJ exhibits moderate inhibition of glucocerebrosidase. See Column 10, lines 56-67 and Table 5. In view of the above, these authors clearly did not appreciate that a combination of NB-DNJ and enzyme augmentation would be of any utility. Indeed, the disclosure of Platt et al. would teach a skilled artisan that such a combination would be contraindicated in a method directed to reducing accumulation of glucosylceramide-containing glycolipids in a patient afflicted with a glycolipid storage-related disorder. Thus, this reference fails to anticipate the methods of the present invention.

The Examiner cites the second full paragraph on page 425 of Platt and Butters as allegedly contemplating a combination therapy. Applicant respectfully disagrees and requests clarification regarding the paragraph that allegedly contemplates combination therapy. Platt and Butters do, however, disclose that glycolipid storage diseases, e.g., Gaucher's disease, may be treated by enzyme replacement therapy using, e.g., glucocerebrosidase, or by substrate deprivation using e.g. NB-DNJ or NB-DGJ. Although Platt and Butters mention in passing the hypothetical concept of a combination therapy, such hypothesizing is limited and utterly lacking in substantive support. Thus, Platt and Butters do not enable the combination of an imido sugar capable of inhibiting glucosylceramide synthase and either glucocerebrosidase or transplanted bone marrow, nor does this reference present any evidence that NB-DNJ and enzyme augmentation act synergistically. Thus, this reference fails to anticipate the methods of the present invention which are directed to the combination of an imido sugar capable of inhibiting glucosylceramide synthase and glucocerebrosidase or bone marrow transplantation.

With respect to the Aerts et al. application, this reference comments in passing that a combination of a glucosylceramidase inhibitor and glucocerebrosidase "may be envisioned" for the treatment of Gaucher's disease. The authors **speculate** that the administration of glucosylceramidase inhibitors may improve the efficacy of enzyme therapy, but provide no evidence to support this assertion. Of note, Aerts et al. do not enable a method for such a combination therapy, nor does this reference present any evidence that an imido sugar capable of inhibiting glucosylceramide synthase and enzyme augmentation can act synergistically. Furthermore, Aerts et al. specifically teach away from the use of NB-DNJ in combination therapy, as it indicates the disadvantage of using NB-DNJ as it is known to inhibit lysosomal glucocerebrosidase (see page 9, lines 1-12). In view of the absence of enabling disclosure

with respect to such combination therapy, lack of any appreciation regarding the synergistic nature of such combinations, and the presence of guidance underscoring that such combinations can be contraindicated, Applicant asserts that this reference fails to anticipate the methods of the present invention.

As is evident from the cited references, there was a significant technical prejudice against combining NB-DNJ and enzyme augmentation for the treatment of glycolipid storage disorders at the priority date of the present application because NB-DNJ was a known inhibitor of glucocerebrosidase (IC_{50} = 0.52mM), see, for example, paragraph [7] of the present specification and Aerts et al. page 9, lines 1-12. See also Priestman et al. (2000, Glycobiology 10:iii-ix), submitted herewith as IDS reference BA. The Examiner's attention is respectfully directed to page v, left column, third paragraph through to the right column, second full paragraph. It is noteworthy that the Priestman et al. reference was published in a peer reviewed journal and thus, was reviewed by independent scientists well versed in the art. That being the case, if the aforementioned prejudice had not existed, the corresponding assertions would have been deleted.

In sum, the present inventors have made the surprising discovery that co-administration of NB-DNJ and enzyme replacement does not compromise the activity of glucocerebrosidase and indeed provides an augmentation of enzyme activity. See Example 2. In addition, the present inventors have determined that the combination of NB-DNJ and enzyme augmentation in the form of bone marrow transplantation shows an unexpected synergistic effect. See Example 3.

Thus, none of the references relied upon by the Examiner (i.e., Platt et al., Platt and Butters, or Aerts et al.) considered either alone (or in combination) would lead a skilled practitioner to the method of the present invention which is drawn to a combination of an imido sugar capable of inhibiting glucosylceramide synthase and either glucocerebrosidase or transplanted bone marrow for 1) reducing accumulation of glucosylceramide-containing glycolipids; 2) maintaining reduced levels of glycolipids; 3) augmenting glucocerebrosidase activity; 4) increasing the rate of glycolipid degradation; or 5) for improving survival in a patient afflicted with a glycoplipid storage-related disorder.

Fees

No additional fees are believed to be necessitated by this amendment. However, should this be an error, authorization is hereby given to charge Deposit Account No. 11-1153 for any underpayment or to credit any overpayment.

Conclusion

It is submitted, therefore, that the claims are in condition for allowance. No new matter has been introduced. Allowance of all claims at an early date is solicited. In the event that there are any questions concerning this amendment, or application in general, the Examiner is respectfully urged to telephone the undersigned so that prosecution of this application may be expedited.

Respectfully submitted,

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Attachments: Second Supplemental Information Disclosure Statement
Petition for a Two Month Extension of Time
Terminal Disclaimer